Journal of the American College of Cardiology Vol. 52, No. 5, 2008

ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.04.027

Day–Night Variation of Acute Myocardial Infarction in Obstructive Sleep Apnea

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Objectives This study sought to evaluate the day–night variation of acute myocardial infarction (MI) in patients with obstructive sleep apnea (OSA).

Background Obstructive sleep apnea has a high prevalence and is characterized by acute nocturnal hemodynamic and neurohormonal abnormalities that may increase the risk of MI during the night.

Methods We prospectively studied 92 patients with MI for which the time of onset of chest pain was clearly identified. The presence of OSA was determined by overnight polysomnography.

Results For patients with and without OSA, we compared the frequency of MI during different intervals of the day based on the onset time of chest pain. The groups had similar prevalence of comorbidities. Myocardial infarction occurred between 12 AM and 6 AM in 32% of OSA patients and 7% of non-OSA patients ($p = 0.01$). The odds of having OSA in those patients whose MI occurred between 12 AM and 6 AM was 6-fold higher than in the remaining 18 h of the day (95% confidence interval: 1.3 to 27.3, $p = 0.01$). Of all patients having an MI between 12 AM and 6 AM, 91% had OSA.

Conclusions The diurnal variation in the onset of MI in OSA patients is strikingly different from the diurnal variation in non-OSA patients. Patients with nocturnal onset of MI have a high likelihood of having OSA. These findings suggest that OSA may be a trigger for MI. Patients having nocturnal onset of MI should be evaluated for OSA, and future research should address the effects of OSA therapy for prevention of nocturnal cardiac events. (J Am Coll Cardiol 2008;52:343–6) © 2008 by the American College of Cardiology Foundation

Obstructive sleep apnea (OSA) is an increasingly prevalent condition that remains underdiagnosed and undertreated (1). OSA may increase the risk of cardiovascular diseases, including hypertension, ischemic heart disease, stroke, heart failure, pulmonary hypertension, and cardiac arrhythmias (2,3). The prevalence of OSA is 2- to 3-fold higher in patients with a history of myocardial infarction (MI) (4).

In the general population, MI and sudden cardiac death (SCD) occur with a diurnal periodicity that peaks between 6 AM and 12 PM (5). In a previous study, we found that SCD was more frequent during the night in OSA patients (6). Mechanisms of SCD could have included MI, stroke, arrhythmias, pulmonary embolus, aortic dissection, or other cardiovascular causes.

Acute nocturnal pathophysiological responses to OSA, including hypoxemia, sympathetic activation, and surges in blood pressure, may lead to plaque rupture, coronary thrombosis, and MI. Should OSA be a trigger of MI, we would expect a peak of onset of symptoms of MI during the night. Whether OSA

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Manuscript received March 25, 2008; revised manuscript received April 28, 2008, accepted April 29, 2008.

JACC Vol. 52, No. 5, 2008
July 29, 2008:343–6

Abbreviations and Acronyms

AHI = apnea–hypopnea index
BMI = body mass index
BP = blood pressure
MI = myocardial infarction
OSA = obstructive sleep apnea
PSG = polysomnography
SCD = sudden cardiac death

patients are more likely to have nocturnal MI has not been previously studied.

Methods

This study was approved by the Institutional Review Board of the Mayo Clinic, and all subjects provided informed consent. We prospectively studied 92 patients admitted with incident MI to our hospital. Although consecutive patients were eligible, recruitment was based on exclusion criteria listed below, on availability of research personnel, and on patients consenting to participate. The exclusion criteria were: patients without typical chest pain, uncertain time of onset of MI, and previous continuous positive airway pressure treatment.

The diagnosis of MI was made by the patients' attending physician and confirmed by the following: increase in creatine-phosphokinase concentration ≥2 times the upper limit of normal and elevation of troponin T activity (>0.03 ng/ml).

The time of onset of MI was determined by each patient's report of the chest pain that prompted hospital admission. This strategy for assessing the time of MI has been previously validated (7).

Table 1 Characteristics of the Study Population at the Time of MI, According to the Presence or Absence of OSA

Characteristics	OSA (n = 64)	No OSA (n = 28)	p Value
Age (yrs)	64 ± 12	57 ± 12	0.02
Male gender (%)	78	75	0.7
Body mass index (kg/m^2)	31 ± 6	28 ± 4	0.01
AHI (events/h)	22 ± 2.1	1.6 ± 0.3	<0.0001
LVEF (%)	51 ± 2	55 ± 2	0.11
Peak CK (U/l)	1,392 ± 296	1,417 ± 264	0.9
Peak CK-MB (ng/ml)	143 ± 23	134 ± 20	0.8
Hypertension (%)	57	57	1
Hypercholesterolemia (%)	67	61	0.6
Diabetes mellitus (%)	25	11	0.1
Prior MI (%)	13	18	0.5
Congestive heart failure (%)	5	0	0.5
Current smoker (%)	27	39	0.2
Systolic BP (mm Hg)*	120 ± 2	116 ± 3	0.2
Diastolic BP (mm Hg)*	69 ± 1	67 ± 2	0.4
Cholesterol (mg/dl)	178 ± 5	161 ± 6	0.06
Triglycerides (mg/dl)	153 ± 14	101 ± 11	0.02
HDL cholesterol (mg/dl)	43 ± 2	41 ± 2	0.4
LDL cholesterol (mg/dl)	108 ± 4.9	101 ± 6.2	0.4
Fasting glucose (mg/dl)	118 ± 4	112 ± 5	0.4

*Blood pressure values at the time of polysomnography.

AHI = apnea–hypopnea index; BP = blood pressure; CK = creatine kinase; CK-MB = creatine kinase-MB isoenzyme; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction, measured within 1 week after myocardial infarction; MI = myocardial infarction; OSA = obstructive sleep apnea.

Table 2 Medications Taken at the Time of Myocardial Infarction, According to the Presence or Absence of OSA

	OSA (n = 64)	No OSA (n = 28)	p Value
Aspirin (%)	35	25	0.4
Beta-blockers (%)	25	29	0.7
ACE inhibitors (%)	16	21	0.5
Statins (%)	35	39	0.7
Calcium antagonists (%)	9	7	1

ACE = angiotensin-converting enzyme; OSA = obstructive sleep apnea.

Every subject underwent comprehensive polysomnography (PSG) at 17 ± 2.4 days after MI, performed with an attended complete overnight polysomnographic monitoring system. Obstructive apneas and hypopneas were classified according to standard criteria (8). An apnea–hypopnea index (AHI) ≥5 established the diagnosis of OSA. All polysomnographic measurements and diagnoses were made blinded to the timing of symptoms of MI.

Statistical analysis. Patients' characteristics are presented as means (± SD) or percentages. Quantitative variables were compared with a 2-tailed *t* test. Qualitative data and the frequency distributions of MI for the 4 6-h intervals of the day between subjects with and without OSA were compared with the chi-square test or Fisher exact test (when expected frequencies below 5 occurred). Intragroup comparisons were conducted to determine the odds ratio of having OSA in patients who had an MI during each 6-h interval compared with the remaining 18 h of the day.

Results

We studied 92 patients (71 men), mean age 61 ± 13 years and body mass index 30 ± 5 kg/m^2. Using a threshold of AHI ≥5 events/h, OSA was present in 70% of patients. Using a more conservative threshold of AHI ≥10 events/h, about one-half (52%) of our patient population was diagnosed with OSA. Patients' characteristics are shown in Table 1. The 2 groups had similar prevalence of comorbidities. There was no difference between groups regarding medication use (Tables 2 and 3).

The diurnal variation in the onset of MI in OSA patients was different from that observed in non-OSA patients (Fig. 1). From 12 AM to 6 AM, the frequency of MI was significantly higher in OSA patients compared with non-OSA patients (32% vs. 7%; p = 0.01). Using a

Table 3 Medications at the Time of the Sleep Study, According to the Presence or Absence of OSA

	OSA (n = 64)	No OSA (n = 28)	p Value
Aspirin (%)	98	89	0.08
Beta-blockers (%)	100	96	0.3
ACE inhibitors (%)	73	78	0.6
Statins (%)	98	93	0.2
Calcium antagonists (%)	3	0	1

Abbreviations as in Table 2.

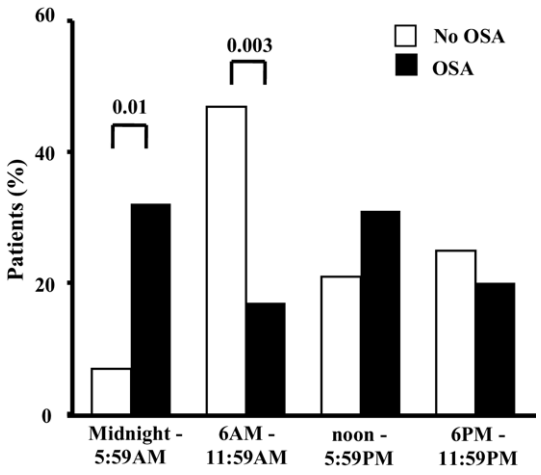

Figure 1 6-h Epochs of MI Occurrence

Day–night pattern of myocardial infarction based on 4 6-h time intervals in OSA (n = 64) and non-OSA (n = 28) patients.

threshold of AHI ≥10 events/h, we observed similar results (33% vs. 14%; p = 0.03). From 6 AM to 12 PM, the frequency of MI was higher in non-OSA patients compared with OSA patients (47% vs. 17%; p = 0.003). Similar results were evident for the analyses based on three 8-h time intervals (Fig. 2). We found no difference in the use of beta-blocker therapy and the frequency of MI during the various intervals of the day.

Patients whose MI occurred between 12 AM to 6 AM had an odds ratio of 6 for having OSA (95% confidence interval: 1.3 to 27.3, p = 0.01). Of 22 patients who had an MI between 12 AM and 6 AM, 20 (91%) had OSA. If we used a more conservative threshold for OSA, the likelihood of nocturnal MI occurring in OSA patients remains significantly higher (73%).

Discussion

The novel finding of this study is that OSA patients have an increased risk of MI between 12 AM and 6 AM compared with non-OSA patients. Our data suggest that OSA may be a trigger for MI, with a striking reversal in the expected diurnal timing of MI onset. Conversely, non-OSA patients had a nadir of MI onset at night and a peak in the morning, similar to the diurnal distribution of MI seen in the general population. Previous studies suggest that beta-blockers (7) and diabetes (9) may attenuate the morning peak of MI. Our findings identify OSA as the first disease condition recognized to actually reverse the usual day–night variation in the incidence of MI.

Obstructive sleep apnea has been implicated in increased risk of MI, stroke, and SCD (10,11). Although OSA patients have a higher frequency of nocturnal ST-segment depression than those without OSA (12,13), it remains unknown whether OSA may directly cause nocturnal MI. Our findings suggest that the pathophysiology of OSA leads to an increased risk of MI during the night.

Several acute pathophysiological mechanisms during sleep in OSA patients may be responsible for their altered diurnal variation of MI. Cessation of airflow results in hypoxemia and hypercapnia, with consequent activation of the chemoreflex (14) and increased sympathetic nerve activity and blood pressure (BP) (15). Obstructed breathing with negative intrathoracic pressures increases cardiac wall stress (16).

Peripheral vasoconstriction and increased cardiac output (caused by changes in cardiac transmural pressures on termination of apneas) lead to dramatic surges in arterial BP. These hemodynamic stresses in the setting of simultaneous hypoxemia and increased myocardial oxygen demand may promote acute nocturnal cardiac ischemia (13,17). OSA is also associated with factors that may increase the risk of nocturnal coronary thrombosis, including platelet activation during sleep (18), elevated fibrinogen levels (19), increased whole-blood viscosity, and decreased fibrinolytic activity (20). These processes may be responsible for the shift in the timing of MI from the morning hours to the night in OSA patients.

Strengths of the current study include, first, its prospective design. Second is the use of complete PSG, interpreted while blinded regarding time of onset of MI. Third, the influence of OSA on timing of MI onset could not be explained by comorbidities or medications, which were similar in both groups. Potential limitations include, first, the inherent uncertainty in identifying the exact timing of onset of an MI. The pathophysiology of coronary plaque rupture and arterial thrombosis is dynamic and occurs over varying time periods before symptoms or signs may manifest. These limitations parallel those of the entire body of

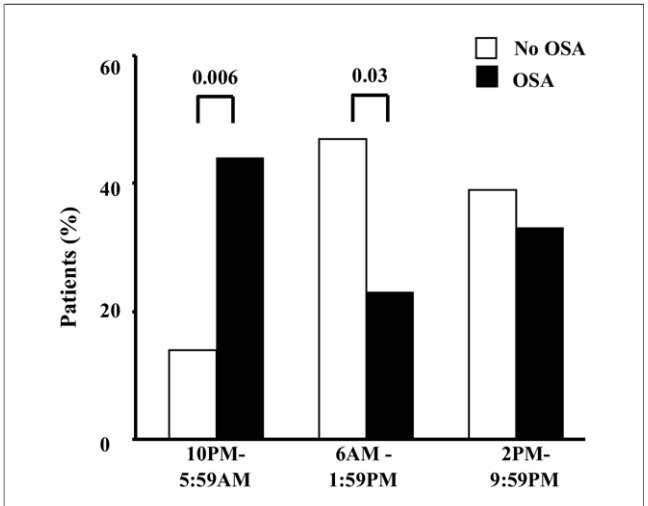

Figure 2 8-h Epochs of MI Occurrence

Day–night pattern of myocardial infarction based on 3 8-h time intervals in OSA (n = 64) and non-OSA (n = 28) patients.

evidence that has demonstrated the timing of MI in the general population and other subgroups (9). Previous studies have shown a strong correlation between the timing of MI, based on cardiac biomarker levels, and the onset of pain (7). Second, based on criteria noted earlier, we did not study every patient admitted with MI. Therefore, our data cannot be used to estimate the overall prevalence of OSA in patients with recent MI. Identifying the prevalence of OSA in the post-MI patient population was not a goal of this study. Nevertheless, the characteristics of our study sample are similar to those of the general MI patient population in Olmsted County (21), and although the prevalence of OSA in our population is relatively high, our findings are comparable to those noted in a prior study of OSA prevalence in the post-MI patient population (22). A third concern relates to whether OSA developed as an acute consequence of MI. Of patients found to have OSA on PSG, 76% had a high risk for OSA as assessed by the Berlin Questionnaire, suggesting that the OSA was indeed likely to have been present before the MI. Furthermore, PSG was conducted when patients were stable. Most important, this limitation cannot account for our findings of a higher nocturnal occurrence of MI in OSA patients. Last, these studies represent survivors of MI, and do not necessarily represent all patients with acute MI.

Conclusions

In summary, we have shown that patients with OSA have an altered diurnal variation of MI, which is consistent with the unique nocturnal pathophysiology of OSA. These findings highlight a potential causative role of OSA in the development of acute coronary syndromes, and suggest that nocturnal MI may contribute to the increased likelihood of nocturnal SCD observed in OSA patients (6). Our data further suggest that those patients who experience the onset of MI during the usual sleep hours should be evaluated for the presence of OSA. Further research is necessary to understand the effects of OSA therapy on modifying the timing of MI in these patients and in altering their overall risk of acute coronary syndromes and SCD.

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REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–39.
2. Malhotra A, White DP. Obstructive sleep apnoea. Lancet 2002;360:237–45.
3. Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004;79:1036–46.
4. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. Chest 1996;109:659–63.
5. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997;79:1512–6.
6. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005;352:1206–14.
7. Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.
8. Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM Manual for the Scoring of Sleep and Associated Events. Rules, Terminology and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine, 2007:45–7.
9. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Circadian variation in the onset of myocardial infarction: effect of duration of diabetes. Diabetes 2003;52:1464–8.
10. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046–53.
11. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034–41.
12. Schafer H, Koehler U, Ploch T, Peter JH. Sleep-related myocardial ischemia and sleep structure in patients with obstructive sleep apnea and coronary heart disease. Chest 1997;111:387–93.
13. Alonso-Fernandez A, Garcia-Rio F, Racionero MA, et al. Cardiac rhythm disturbances and ST-segment depression episodes in patients with obstructive sleep apnea-hypopnea syndrome and its mechanisms. Chest 2005;127:15–22.
14. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation 1999;99:1183–9.
15. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–904.
16. Floras JS, Bradley TD. Treating obstructive sleep apnea: is there more to the story than 2 millimeters of mercury? Hypertension 2007;50:289–91.
17. Mooe T, Franklin KA, Wiklund U, Rabben T, Holmstrom K. Sleep-disordered breathing and myocardial ischemia in patients with coronary artery disease. Chest 2000;117:1597–602.
18. Sanner BM, Konermann M, Tepel M, Groetz J, Mummenhoff C, Zidek W. Platelet function in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000;16:648–52.
19. Chin K, Ohi M, Kita H, et al. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996;153:1972–6.
20. Rangemark C, Hedner JA, Carlson JT, Gleerup G, Winther K. Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients. Sleep 1995;18:188–94.
21. Gerber Y, Jacobsen SJ, Killian JM, Weston SA, Roger VL. Participation bias assessment in a community-based study of myocardial infarction, 2002–2005. Mayo Clin Proc 2007;82:933–8.
22. Mehra R, Principe-Rodriguez K, Kirchner HL, Strohl KP. Sleep apnea in acute coronary syndrome: high prevalence but low impact on 6-month outcome. Sleep Med 2006;7:521–8.

Key Words: obstructive sleep apnea ■ myocardial infarction ■ day–night variation.